REMARKS

Status of the Claims

Claims 1, 3-4, 6-8, 10, 27, and 29-30 were pending in the present application. Applicants have canceled claim 3 and have amended claims 1, 8, 27, and 30, without prejudice to Applicants' right to pursue their original subject matter in the present application and in related applications. Upon entry of this amendment, claims 1, 4, 6-8, 10, 27, and 29-30 will be pending and are presented for consideration.

Claim Amendments

Applicants have amended claim 1 to recite a mutation or a deletion at one or more amino acids selected from the group consisting of Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, and Asn_{297}, said mutation or deletion reducing binding affinity for an Fc receptor. Support for this amendment can be found throughout the application as originally filed, for example, at least in original claim 3.

Applicants have amended claim 8 to insert appropriate punctuation.

Applicants have amended claim 27 to recite "an IgG4 CH2 domain" rather than "a portion of an IgG4 CH2 domain." Support for this amendment can be found throughout the application as originally filed.

Applicants have amended claim 30 to delete unnecessary words for consistency with amended claim 1.

Applicants submit that these amendments introduce no new subject matter.

Interview Summary

Applicants would like to the thank the Examiner and her supervisor for discussing this case during the telephonic interview of March 28, 2005. During the interview, while no conclusion was reached, Applicants discussed the references "Gillies" and "Gray," cited *infra*, and ways that the rejection under 35 U.S.C. § 103(a) might be overcome.

Claim Rejections under 35 U.S.C. § 112

The Office action rejected claims 1, 6-8, 10, 27, 29, and 30 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while being enabling for nucleic acids encoding fusion proteins having decreased Fc receptor binding wherein the CH2 domain of IgG1 was deleted or mutated at Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, Asn_{297}, or Pro_{331}, or where the CH2 domain of IgG3 was deleted or mutated at Leu_{281}, Leu_{282}, Gly_{283}, Gly_{284}, Asn_{344}, or Pro_{378}, or where the entire IgG4 CH2 domain was used in place of IgG1 CH2, does not reasonably provide enablement for nucleic acids encoding fusion proteins having any mutation or deletion in the CH2 domain, or any portion of an IgG4 CH2 domain. Applicants respectfully traverse this rejection.

To expedite prosecution of this application, claim 1 has been amended without prejudice to recite a mutation or a deletion at one or more amino acids selected from the group consisting of Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, and Asn_{297}. Consequently, Applicants respectfully request that the rejection of claims 1, 6-8, 10, 29, and 30 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn in view of the amendment to claim 1.

To expedite prosecution of this application, claim 27 has been amended without prejudice to recite a fusion protein comprising a variable domain and an IgG4 CH2 domain. Consequently, Applicants respectfully request that the rejection of claim 27 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn in view of the amendment.

The Office action also rejected claims 1, 6-8, 10, 27, 29, and 30 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while disclosing fusion proteins comprising the entire IgG4 CH2 domain, and mutations or deletions at Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, Asn_{297} and Pro_{331} of the IgG1 constant region, does not disclose sufficient species for the broad genus of any genetic modification that results in decreased Fc receptor binding.

Claim 1 has been amended without prejudice to recite a mutation or a deletion at one or more amino acids selected from the group consisting of Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, and Asn_{297}. Consequently, Applicants respectfully request that the rejection of claims 1, 6-8, 10, 29, and 30 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn in view of the amendment to claim 1.

Claim 27 has been amended without prejudice to recite the fusion protein comprising a variable domain and an IgG4 CH2 domain. Consequently, Applicants respectfully request that the rejection of claim 27 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn in view of the amendment.

Claim Rejections under 35 U.S.C. § 103

Claims 1, 3, 6-8, 10, 27, 29, and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gillies *et al.* (1993, *Bioconjugate Chem.* 4:230-235, hereinafter "Gillies") in view of Gray *et al.* (U.S. Patent No.6,444,792, hereinafter "Gray"). Applicants respectfully traverse the rejection as applied to the pending claims.

Claim 1 and those depending therefrom (6-8, 10, 29, and 30) are directed to a region of a gene construct encoding an antibody-based fusion protein including, at its 5' end, nucleotides encoding at least a portion of an IgG1 CH2 domain, with a mutation or a deletion reducing binding affinity for an Fc receptor, and at the 3' end, nucleotides encoding a non-Ig protein.

As acknowledged by the Examiner, while Gillies teaches a fusion protein in the appropriate orientation *i.e.* Ig-IL-2, Gillies does not teach mutations that would increase the serum half-life of the Ig-IL-2 fusion protein. However, the Examiner suggests there is a motivation to combine Gillies with Gray to produce the applicant's claimed invention because Gillies allegedly wished to improve the serum half-life of Ig-IL-2, and Gray allegedly teaches modifications to fusion proteins that increase serum half life by modifying Fc receptor binding. However, Applicants respectfully submit, that Gray does not in fact teach that the mutations of his invention result in an immunoglobulin fusion protein with an improved serum half life. Consequently, Applicants submit that the deficiencies of Gillies cannot be remedied by the addition of Gray.

Firstly, while the Office action points out that Gray teaches "the CH2 domain may be modified to reduce interactions with Fc receptors" and that "such modifications are useful for decreasing complement activation and phagocytosis (Col. 9, lines 60-64; Col. 4, lines 24-33)," nothing in Gray teaches or suggests that these modifications result in immunoglobulin fusion proteins with longer serum half-lives. In fact, Gray states only that the CTLA4-immunoglobulin

fusion proteins according to his invention, which may be mutated to reduce effector functions, "display a long plasma half-life *in vivo* (Col. 9, lines 33-35)," not a longer half-life than fusion proteins without the mutations. Given that protein constructs containing an Fc portion were known by those skilled in the art to have already long serum half-lives, it is not surprising that Gray's mutated CTLA4-Ig fusion protein, which contains an Fc portion, has a long serum half-life. There is no indication that Gray appreciated or taught that mutations to the Fc region can result in lengthened or improved serum half-lives.

Further evidence that Gray does not teach immunoglobulin fusion proteins with mutations that lengthen or improve serum half-life is shown by the data from his pharmacokinetic studies. In his analysis, Gray compares the serum half-life of wild type CTLA4-IgG1 and a version of CTLA4-IgG4 mutated to contain nucleotide changes in the CH2 domain to replace amino acids thought to be required for IgC binding to Fc receptors, and complement activation (see Gray, col. 30, lines 21-29; and col, 40, lines 9-39). Despite the fact that wild-type IgG1 is known in the art to have high levels of Fc receptor binding, and that IgG4 is known in the art to have reduced levels of Fc receptor binding, which would be further reduced by the mutations of Gray, Gray concluded that "both CTLA4IgG1 and [mutated] CTLA4IgG4 have **similar clearance rates**...indicating a serum half life of approximately 4 hours" (col. 40, lines 35-39). Thus, Gray concluded that there was **no difference in the serum half-lives** of the two fusion proteins, despite the IgG1 and IgG4 fusion proteins having differing affinities for Fc binding, as known in the art. In other words, Gray found that the mutations to the CH2 domain that reduced Fc receptor binding did **not increase the serum half-life** of the modified Ig fusion protein. Moreover, a closer look at Gray's data showed that the β phase half-life of the wild type CTLA4-IgG1 was **longer** than the mutated CTLA4-IgG4, **not shorter.** In fact, the wild-type fusion protein had a β phase half-life of 288 minutes compared to 214.2 minutes for the mutant variety (see col. 40, lines 31 and 34). Consequently, Gray's data does not show that reducing Fc receptor binding increases the serum half-life of Gray's fusion protein. Therefore, Applicants respectfully submit that a person skilled in the art would not be motivated to modify the fusion protein of Gillies according to the teachings of Gray because Gray does not teach or appreciate that the serum half-life of the modified fusion protein would in fact increase.

Furthermore, Applicants submit that the deficiencies of Gillies cannot be remedied by the teachings of Gray because Gillies teaches away from a combination with Gray. In particular, Gillies fusion protein is designed to perform an immunostimulatory function. In fact, the orientation of Gillies' Ig-IL-2 fusion protein is designed to allow the C-terminal IL-2 moiety to target T-cells, while the variable domain is left able to bind antigen on tumor cells. This orientation is important so that the tumor killing activity of T-cells can be localized at the tumor site. However, not only does Gray teach a fusion protein in the opposite orientation of Gillies (the CTLA4 moiety is fused to the N-terminus), Gray also teaches that his fusion protein comprising CTLA4 is designed to be immunoinhibitory (see col. 3, lines 26-32). In particular, Gray teaches that fusion proteins with reduced effector functions "are likely to have improved immunoinhibitory properties" (see col. 3, lines 35-45). Applicants submit that there was no motivation to incorporate Gray's modifications into Gillies' immunostimulatory Ig-IL2 fusion protein. Consequently, Applicants submit that even in combination, Gray and Gillies cannot render the claimed invention obvious.

For the reasons outlined above, Applicants respectfully request that the rejection of claim 1, and dependent claims 6-8, 10, and 29-30 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Claim 27 is directed to an antibody-based fusion protein comprising a variable domain and a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein. As discussed above, the Office action claims that there is a motivation to combine Gillies and Gray to create the applicants claimed invention because Gray allegedly teaches modifications to fusion proteins that increase serum half-life, and Gillies allegedly was trying to improve the serum-half life of Ig-IL-2 in order to improve targeting of IL-2 to tumor cells. However, Applicants respectfully submit that there is no motivation to combine Gillies and Gray to produce the applicants' claimed invention because Gray does not, in fact, teach that an antibody-based fusion protein comprising an IgG4 CH2 domain would have a longer circulating half-life than an IgG1-containing fusion protein. Applicants incorporate herein the arguments made *supra*, in relation to the rejection of claim 1 under 35 U.S.C. § 103(a). For

these reasons, Applicants respectfully request that the rejection of claim 27 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the pending claims presented for consideration herein are in condition for allowance. If the Examiner would like to discuss any outstanding issues, she is invited to telephone the undersigned.

Respectfully submitted,

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